**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| In re Application of **Schwendeman, *et al.*** | Examiner: Blessing M. Fubara |
| Serial No.: 09/738,961 | Group Art Unit: 1615 |
| Filed: December 15, 2000 | |
| For: **METHODS FOR STABILIZING BIOLOGICALLY ACTIVE AGENTS IN BIODEGRADABLE CONTROLLED-RELEASE POLYMERS** | Attorney Docket No.: 22727/04045 |

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, DC 20231

## DECLARATION UNDER 37 CFR § 1.132

Dear Sir:

I, Dr. Steven P. Schwendeman, an inventor of the above-identified application state as follows:

1. I received a Bachelor of Science in Engineering Degree in Chemical Engineering in 1986 from the University of Michigan, and a Doctor of Philosophy Degree in Pharmaceutics from the University of Michigan in 1992. I was a postdoctoral associate or NIH postdoctoral fellow at Massachusetts Institute of Technology between 1992 and 1995. I am the inventor or co-inventor of 5 US patents and patent applications and the author or co-author of 14 publications relating to pharmaceutics in general, and 63 publications

relating specifically to biodegradable controlled-release polymers. For the past 2 years, I have been Assistant Professor of Pharmaceutical Sciences at the University of Michigan, where I lead a research group that examines the underlying molecular mechanisms responsible for the instability of substances, particularly proteins, when encapsulated in controlled release polymers, principally copolymers derived from lactic and glycolic acids. Previously, I was an Assistant Professor of Pharmaceutics at The Ohio State University for 5 years, where I led a research group that also focused on the study of controlled-release polymers and the molecular mechanisms responsible for the instability of the substances encapsulated therein. I am on the editorial board of *Journal of Pharmaceutical Sciences* and *PharmSci*. I have served as a peer reviewer for papers in the relevant areas of expertise in several journals including *Nature*, *Nature Biotechnology*, *Proceedings of the National Academy of Sciences USA*, *Pharm. Res.*, *J. Pharm. Sci.*, and *J. Controlled Release*.

2. I have read the Cleland reference cited by the Examiner, US Pat. No. 5,643,605 (hereinafter referred to as "Cleland"). I have read and I am familiar with the claims in the present application.

3. The buffers used in Cleland are different from the basic additives, or antacids of the above-mentioned application. Cleland, column 9 lines 35-40, shows the use of weakly acidic and/or weakly basic buffers, namely phosphate, Tris, citrate, succinate, acetate, and histidine, to maintain the pH of the aqueous solution or suspension during the encapsulation of the polypeptide into the polymer microspheres. These buffers dissolve completely in solution. The Cleland buffers are used in the formulation to maintain a desired pH or narrow pH range, e.g. usually within one pH unit of the buffer's pKa(s). Depending on the buffer used during encapsulation, the desired pH in the aqueous solution or suspension may be acidic, basic, or neutral. The buffer used in the Cleland solution or suspension may be encapsulated into Cleland's particles. However, because of their high solubility, all of the buffers mentioned by Cleland are susceptible to diffusing out of the polymeric delivery system (e.g. during the initial burst) and, therefore, may not be available to neutralize the acids that accumulate in the polymeric delivery system during degradation *in situ* for long periods. In addition, the Cleland

buffers are weak acids or weak bases; that is, they do not completely dissociate in solution. Instead, they establish an acid-base equilibrium where both the weak acid/base and its conjugate base/acid are present in similar concentrations. In contrast, strong acids and bases, which dissociate completely in solution, do not establish such an acid-base equilibrium. There is nothing in Cleland to suggest that the buffers discussed are intended for, or are useful in, preventing the highly acidic microclimate pH (e.g. pH less than 3) in the polymer from occurring.

4. The basic additives or antacids of the present invention are basic salts that are insoluble or poorly soluble in an aqueous solution. These insoluble basic salts are not good buffers for use during encapsulation. According to the present invention, very small particles of these insoluble salts are encapsulated into the polymer microspheres and do not significantly solubilize until 1) the polymer is undergoing degradation *in situ*, and 2) there are acidic conditions in the polymer microclimate. Both criteria must be met before the basic additives, or antacids, will significantly dissolve, and are thus able to diffuse out of the polymer. During degradation of the polymer *in situ*, the basic additives dissolve only under acidic conditions and thereby neutralize acidic degradation products at localized sites within the polymer's microclimate. If the polymer microclimate is not acidic, the basic additive, or antacid, particles will be retained, undissolved, in the polymer.

5. The amount of polyethylene glycol (PEG) used in the Cleland application is different from the amount claimed in the present application. Cleland shows a mass range of PEG to polypeptide as 100:1 to 1:100, preferably 1:1 to 1:10. Cleland adds PEG to directly affect the polypeptide molecule, stating that "preferred ratios are chosen on the basis of an excipient concentration which allows maximum solubility of polypeptide with minimum denaturation of the polypeptide." (Cleland, Column 9, lines 20-23).

6. In the present invention, claim 1, as amended, specifies that a pore-forming agent is added to the polymer at a range of about 10% to about 30% (w/w) based on the polymer, wherein the pH is maintained at a value between 3 and 8 during biodegradation. The pore-forming agent of the present invention is added to directly affect the polymer during

degradation. The specification teaches that the preferred pore-forming agent is PEG. The PEG to polymer ratio of the present invention is from about 10:90 to about 30:70. By adding PEG to the polymer microspheres at this particular ratio, an unexpected result is achieved—the pH in the polymer microclimate is maintained in the range of from about 3 to about 8. Using about 10% to about 30% PEG, as claimed in the present invention, is necessary for achieving the desired effect, i.e. maintaining the pH of the polymer microclimate from about pH 3 to about pH 8 for a period of about four weeks. Adding PEG in the amount taught in Cleland's preferred range will not necessarily achieve this desired result. Moreover, Cleland teaches the use of PEG to produce a direct effect on the polypeptide, i.e. stabilization during encapsulation. The present invention, on the other hand, is using PEG to produce a direct effect on the polymer, and thereby produce an indirect effect on the biologically active agent, i.e. protecting the biologically active agent from the destabilizing effects of the highly acidic degradation products that occur during biodegradation in a subject, or in physiological buffer.

7. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date 8-13-02

Dr. Steven P. Schwendeman